Cancer Treatment Reviews 40 (2014) 48–59

Contents lists available at SciVerse ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

Stereotactic radiosurgery in the treatment of brain metastases: The current evidence

Bodo Lippitz [a,b,*], Christer Lindquist [b], Ian Paddick [b], David Peterson [b,c], Kevin O'Neill [b,c], Ronald Beaney [b,d]

[a] Gamma Knife Center, Karolinska University Hospital, Stockholm, Sweden
[b] Gamma Knife Centre, Bupa Cromwell Hospital, London, United Kingdom
[c] Charing Cross Hospital, London, United Kingdom
[d] Guy's and St. Thomas' NHS Foundation Trust, United Kingdom

ARTICLE INFO

Article history:
Received 24 September 2012
Received in revised form 8 May 2013
Accepted 8 May 2013

Keywords:
Brain metastases
Radiosurgery
Treatment results
Gamma Knife
Linac

ABSTRACT

Chemotherapy has made substantial progress in the therapy of systemic cancer, but the phar-macological efficacy is insufficient in the treatment of brain metastases. Fractionated whole brain radiotherapy (WBRT) has been a standard treatment of brain metastases, but provides limited local tumor control and often unsatisfactory clinical results. Stereotactic radiosurgery using Gamma Knife, Linac or Cyberknife has overcome several of these limitations, which has influenced recent treatment recommendations. This present review summarizes the current literature of single session radiosurgery concerning survival and quality of life, specific responses, tumor volumes and numbers, about potential treatment combinations and radioresistant metastases.

Gamma Knife and Linac based radiosurgery provide consistent results with a reproducible local tumor control in both single and multiple brain metastases. Ideally minimum doses of ≥18 Gy are applied. Reported local control rates were 90–94% for breast cancer metastases and 81–98% for brain metastases of lung cancer. Local tumor control rates after radiosurgery of otherwise radioresistant brain metastases were 73–90% for melanoma and 83–96% for renal cell cancer. Currently, there is a tendency to treat a larger number of brain metastases in a single radiosurgical session, since numerous studies document high local tumor control after radiosurgical treatment of >3 brain metastases. New remote brain metastases are reported in 33–42% after WBRT and in 39–52% after radiosurgery, but while WBRT is generally applied only once, radiosurgery can be used repeatedly for remote recurrences or new metastases after WBRT. Larger metastases (>8–10 cc) should be removed surgically, but for smaller metastases Gamma Knife radiosurgery appears to be equally effective as surgical tumor resection (level I evidence). Radiosurgery avoids the impairments in cognition and quality of life that can be a consequence of WBRT (level I evidence). High local efficacy, preservation of cerebral functions, short hospitalization and the option to continue a systemic chemotherapy are factors in favor of a minimally invasive approach with stereotactic radiosurgery.

Introduction

According to conservative estimates about 8% of cancer patients will develop brain metastases,[1] which often cause the leading symptoms. Chemotherapy has significantly improved the prognosis of patients with cancer but generally fails in the treatment of brain metastases. When brain metastases were considered inoperable and were left untreated, the median survival was only 51 days.[2] An effective therapy and local tumor control is paramount for the prognosis the quality of life.

In practice, conventional fractionated whole brain radiotherapy (WBRT) is still frequently applied as a standard therapy of brain metastases,[3] but side effects and lack of sustained local efficacy could outweigh potential benefits: The median survival of patients with brain metastases treated with WBRT ranges between 2.8 and 5.4 months[4–12] and was less than 4.5 months in 8 out of 9 studies in 1925 out of 1971 reported patients. In patients with adverse prognostic features there was no significant difference between best supportive care and 20 Gy WBRT and only slight and clinically irrelevant differences in the 30 Gy WBRT group (median 2.2 vs. 1.7 months).[13] These results match the recently published interim data from the QUARTZ Trial (Quality of Life after Radiotherapy for

* Corresponding author. Address: Gamma Knife Centre, Bupa Cromwell Hospital, Cromwell Road, London SW50TU, United Kingdom.
E-mail addresses: bodo.lippitz@cromwellhospital.com, bodolippitz@me.com, bodo.lippitz@karolinska.se (B. Lippitz).

0305-7372
http://dx.doi.org/10.1016/j.ctrv.2013.05.002

Brain Metastases), a randomized phase III trial of patients with inoperable NSCLC brain metastases that showed a median survival of 49 days after optimal supportive care plus WBRT.[2]

On the other hand, WBRT must be considered insufficient in patients with a better systemic prognosis, since prospective and randomized studies showed that WBRT provided only limited local control over the treated brain metastases with complete or partial responses in 24–55%.[14,15] WBRT in brain metastases of colorectal cancer (3 Gy $\times$ 10) achieved a local control of 17% at 6 months.[16] In clinical practice, chemotherapeutical regimens are often discontinued during fractionated radiotherapy of brain metastases.

The application of focal radiation using Gamma knife or Linac based stereotactic radiosurgery (SRS) has changed these previously rather negative perspectives in a fundamental way. Reproducible tumor control after radiosurgery underlines that physically focused and stereotactically applied radiation can overcome several limitations of fractionated radiotherapy. This insight has significantly influenced treatment recommendations[17] and guidelines that have recently been published to define the criteria for treatment of brain metastases from a surgical,[18] radiotherapeutical[19,20] and radiosurgical[21] perspective. Larger brain metastases with a clinically relevant mass effect should be removed surgically as two prospectively randomized trials found significantly improved survival and functionally independent survival after surgical resection when compared with fractionated radiotherapy alone[22,23]. Single session radiosurgery in larger brain metastases is generally not recommended due to the increased risk of a later formation of edema with associated delayed side effects.

In practical terms radiosurgery is still an unusual treatment, as only 6.1% of 7684 patients with non-small cell lung cancer who were diagnosed with brain metastases in the US between 2000 and 2007 had billing codes for stereotactic radiosurgery[24]. Similarly, an international online practice survey that was answered predominantly by radiation oncologists, showed that 78% of respondents would still use WBRT alone for initial treatment of two to four brain metastases in patients with a KPS of 70 and active extra-cranial disease [3]. The use of radiosurgery however, was significantly associated with increasing year of diagnosis, higher socioeconomic status and admission to a teaching hospital [24].

Several most relevant statements defining the role of radiation therapy in the treatment of brain metastases that have recently been formulated in an American Society for Radiation Oncology evidence-based guideline[20] reflect a changing paradigm and are summarized below:

1. The addition of fractionated whole brain radiotherapy (WBRT) after surgical resection of brain metastases does not improve overall survival or duration of functional independence, but improves treated brain metastasis control and overall brain control.[20,25,26]
2. In patients with good prognosis and single brain metastasis (<3 cm), either surgery or radiosurgery may be considered.[20]
3. Selected patients with brain metastasis(es) may be treated with radiosurgery alone.[20]
4. Radiosurgery boost added to WBRT in patients with multiple brain metastases and good prognosis improves control over treated brain metastases as compared with WBRT alone.[20,27,28]
5. Two randomized trials showed that omission of WBRT after radiosurgery is associated with better neurocognitive outcomes[29,20] and with better health related quality of life.[30]
6. The randomized trial RTOG 9508[31] found an improvement in KPS and decreased steroid use at 6 months with the use of radiosurgery boost added to WBRT, but
7. WBRT alone may be considered, as there is no survival advantage with radiosurgery added to WBRT in patients with multiple brain metastases.[20]

Brain tumour control can be essential for the neurologic integrity and quality of life, but may not always have a direct impact on the patient's survival, since the patient's outcome is determined by the characteristics and the status of the systemic disease [32–36]. In this situation chemotherapy regains an important role, since it is generally not disrupted for single session radiosurgery. The validation of treatment success in the therapy of brain metastases can be complex, since local control of the treated metastasis is not generally measured in the radiotherapeutical literature and the comparison of survival rates seems to be insufficient for the determination of the optimal treatment: Recent studies defined the negative outcome for patients who were treated with best supportive care only, hence emphasizing the need for effective treatment of brain metastases.[2,13] However, several prospective randomized studies demonstrated that the overall survival of patients with multiple metastases appeared to be relatively unaffected by the local control of brain metastases: In a recent EORTC study the overall survival did not differ between the surgery/radiosurgery arms, when WBRT was added or omitted with a median survival of 10.9 months in the observation arm and 10.7 months in the WBRT arm, although WBRT reduced the probability of relapse at initial sites for the patients treated with radiosurgery from 31% to 19% and after surgery from 59% to 27% (at 2 years), respectively.[26] Similarly, Aoyama showed in a randomized trial that median survival was 7.5 months in the WBRT plus stereotactic radiosurgery (SRS) group and 8.0 months for radiosurgery alone ($P = .42$), although the 12-month brain tumour recurrence rate was 46.8% in the WBRT plus SRS group and 76.4% for SRS alone group ($P < .001$) and the actuarial local tumour control rate at 12 months was 88.7% in the WBRT plus SRS group and 72.5% in the SRS-alone group ($P = .002$).[28] Patchell had shown for patients with single brain metastases who were treated with complete surgical resections and postoperative WBRT, or no further treatment, that recurrence of tumor anywhere in the brain was less frequent in the radiotherapy group (18%) than in the observation group (70%), but that there was no significant difference between the groups in overall length of survival or the length of time that patients remained functionally independent.[25] In another prospective randomized study, patients with two to four brain metastases were randomized to initial brain tumour management with WBRT alone or WBRT plus Gamma Knife radiosurgery. The study was stopped at an interim evaluation at 60% accrual, since the rate of local failure at 1 year was 100% after WBRT alone but only 8% in patients who had boost radiosurgery. Although there was a trend in improved median survival in the radiosurgery group, the difference was not significant (11 vs. 7.5 mo).[27]

The vast majority of the scientific evidence has been published on single session radiosurgical treatments, and the current review focuses entirely on this treatment form, although the American Society for Therapeutic Radiology and Oncology (ASTRO), the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) agreed that stereotactic radiosurgery typically is performed in a single session, but can be performed in up to five sessions.[37,38] Despite this definition, it still remains to be scientifically proven that single and multiple session radiosurgery are clinically equivalent.

The previously simplistic competition between single treatment technologies has been replaced by comprehensive clinical questions concerning treatment paradigms: WBRT as routine therapy for brain metastases is being questioned with all resulting pros and cons. Highly focused single session radiation is developing as a new standard. The role of hypofractionated radiosurgery will have to be defined and is not discussed in the current review. Common knowledge is changing and more differentiated questions remain to be addressed. The present review attempts to summarize the current literature concerning single session radiosurgery according to relevant clinical issues concerning survival, quality of life, specific responses, tumor volumes and numbers, about potential treatment combinations and radioresistant metastases also with respect to standard fractionated radiotherapy. Not all questions can be answered by a mere comparison of survival rates. The ongoing discussion requires a detailed evaluation of the evidence in all clinical aspects.

Stereotactic radiosurgery

The principle of radiosurgery implies concentrating radiation within a tumor while avoiding radiation of the surrounding healthy tissue (Fig. 1). The Gamma Knife achieves this by mechanical focusing of ca 200 radiation sources, which allows shaping of a defined irradiated volume in the brain. In the stereotactic Linear Accelerator (Linac) the radiation beam is shaped by a set of leaves usually made of a tungsten alloy, the multi-leaf collimator. The position of each leaf is computer-controlled in order to match the geometry of the irradiated lesion. The Cyberknife consists of a small linear accelerator mounted on an industrial robot. The Cyberknife's robotic arm directs small beams of radiation from multiple angles that converge upon the tumor. Shaping of the radiation field is achieved by a high number of different trajectories. The necessary precision of target localization requires a stereotactic MRI or CT study before radiosurgery and a stereotactic frame fixation (for Linac and Gamma Knife). Radiation doses are expressed as "prescription doses" or "minimum doses", reflecting the dose applied to the tumor periphery. Generally, prescription doses of 18–25 Gy are applied in radiosurgery for brain metastases. In Gamma Knife treatments this minimum dose commonly corresponds to 50% of the maximally applied dose (50% isodose) resulting in an inhomogeneous dose distribution within the tumor, with maximum doses ranging between 36 and 50 Gy.

Technical accuracy of stereotactic radiosurgery

In the recent Gamma Knife model (Perfexion), the accuracy of the mechanical versus radiation isocentre was found to be 0.05 mm.[39] Including the geometrical error from implementation of imaging data, the total error in the Gamma Knife system was calculated to be 0.48 ± 0.23 mm.[40] For the Cyberknife, the ideal dynamic alignment margins that accommodate for the detection and correction precision[41,42] have recently been calculated to be 1.5 mm.[43] The patient is not frame fixated during the Cyberknife treatment, hence the accuracy of the treatment depends on the frequency of X-ray based position control measurements, which are necessary to compensate for the patient's involuntary movements. With a frame-based technique, such as the Gamma Knife or a Linac, precision is easier to determine using phantoms since patient movements are mechanically avoided. Phantom studies with a stereotactic Linac have shown that a CT localized target can be irradiated with a positional accuracy of 0.8 mm in any direction with 95% confidence.[44]

Radiation conformity

Radiosurgery avoids the irradiation of healthy tissues. The closer the prescription dose is matched to the treated target and the steeper the dose gradient around the target, the less normal tissue is irradiated. This matching of the dose to a 3-dimensional target is generally quantified using the conformity index, which reflects the amount of normal tissue within the prescription isodose (Fig. 1). A simplified conformity index is the ratio of prescription volume to target volume, which would ideally be one, if no healthy tissue were irradiated. Polymer gel measurements verified the planned dose distribution in the most recent Gamma Knife models (Perfexion) with a conformity of 1.17.[45] For stereotactic Linac radiosurgery this conformity index has been reported to range from 2.7[46] to 1.8 for the micromultileaf collimator.[47] Due to its isocentric planning arrangement it is possible for a Gamma Knife to treat many targets such as multiple brain metastases in one single session, which can be technically challenging for Linac and Cyberknife.

Extracranial doses vary depending on the technology used. Due to effective shielding, Gamma Knife doses decreased steeply with distance from the treated brain, delivering only 13 mSv at the lower pelvis in comparison to 117 and 132 mSv during CyberKnife treatments.[48] Further reduction of extracranial doses has been shown in the recent Gamma Knife model Perfexion.[49]

Clinical efficacy

The first cases of stereotactic percutaneous single dose radiosurgical treatments for cerebral metastases had been published

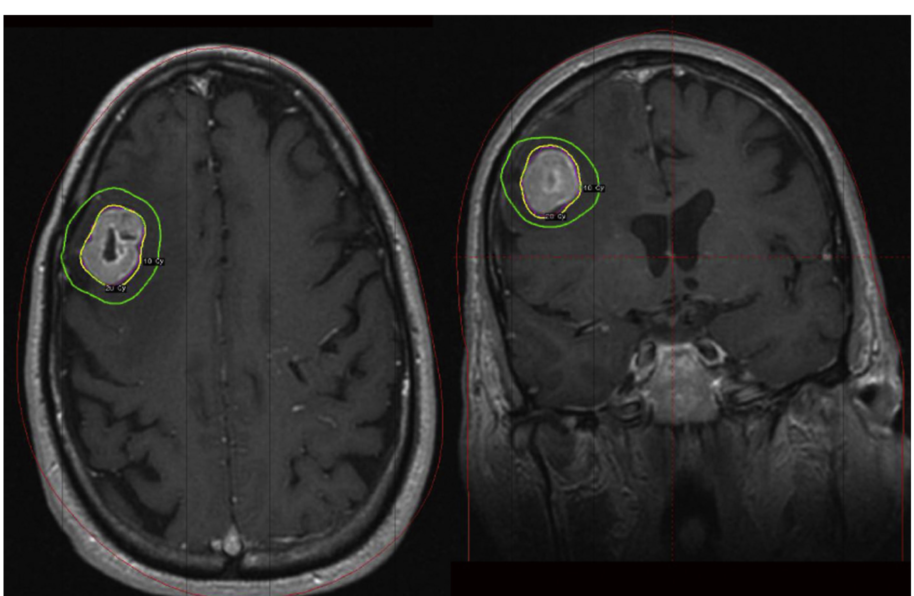

Fig. 1. Typical radiosurgical dose plan (Gamma Knife) for a right frontal metastasis with high radiation conformity to the target showing the 20 Gy prescription isodose (yellow line) and the 10 Gy isodose (green line).

by Sturm in 1987 after treatment with a stereotactic linear accelerator[50] and 1989 by Lindquist after treatment with Gamma Knife.[51] Since then an estimate of more than 200,000 radiosurgical treatments for brain metastases have been carried out, the vast majority with Gamma Knife.

A wide range of retrospective and prospective Gamma Knife studies with more than 4800 published patients with brain metastases provide consistent and reproducible results with an average local tumor control between 84% and 97%[52–76] (Fig. 2). The treatment with stereotactic Linac is often applied with lower maximum doses when compared to the Gamma Knife but the clinical results in brain metastases appear to be similar.[31] Local control of metastases treated with Linac is achieved in 85–91%[77–79] and the 1-year tumor control rates range between 69% and 81%[80,81] with lower local control (60%) in tumors larger than 2 cm.[82] So far there are too few publications on Cyberknife treatment for brain metastases to allow a comparison, since the technology is relatively new but recent studies showed a similar local control of brain metastases.[83,84]

Chidel found no difference in local or distant relapse of brain metastases among patients treated with Gamma Knife compared with stereotactic Linac,[85] but systematic comparisons between radiosurgical treatment facilities are lacking. Detailed analyses concerning differences in local control, adverse effects, practicability and number of treatable metastases will have to be carried out, but based on the currently available evidence it has to be assumed that in the treatment of brain metastases clinical results will be similar in various applied technologies.

Multivariate analysis indicated that longer freedom from progression was significantly associated with higher radiosurgical dose; local tumor control was superior for metastases treated at minimum doses of 18 Gy or higher.[71] A similar Gamma Knife study showed that a margin dose of 18 Gy was more likely to provide tumor reduction and resolution of peritumoral oedema,[86] which was also demonstrated for Linac treatments.[87] Brain metastases tend to shrink gradually after radiosurgery; the perifocal oedema disappears after several weeks. Metastases that are generally resistant to fractionated external beam radiation, such as melanoma or renal cancer, are successfully treated by stereotactic radiosurgery, which has lead to a paradigm change in the therapy of these tumors [55,61,88].

The tumor volume is the primary limiting factor in radiosurgery since the volume of the irradiated healthy brain in the penumbra of the metastasis increases when larger metastases are treated. This can result in formation of a local oedema around the irradiated target, typically 6–9 months after radiosurgery. This effect is generally transient, but may require steroid medication and in rare cases, a surgical intervention. Adverse radiation effects are generally seen in larger metastases or unconformal treatments and are uncommon when metastases smaller than 2.5 cm are treated.

Breast cancer

Fractionated WBRT for brain metastases of breast cancer achieved only limited local control with intracranial failure after a median of 3–5 months.[89,90] When radiosurgery was used as salvage treatment of tumor recurrence after WBRT, the median survival was 10.3–14 months[91–93] (Fig. 3).

Four retrospective analyses after Gamma Knife treatment of breast cancer metastases with a combined 599 patients reported high local tumor control rates between 90% and 94%.[52,54,93,94] The prognosis of patients with brain metastases of breast cancer seems to be slightly superior when compared to other groups of cancer patients with a median survival between 10 and 16 months.[54,94–97] Patients in RPA class I, II, and III survived 34.9, 9.1, and 7.9 months, respectively.[94] The improvements of chemotherapy for breast cancer patients underline the necessity for an equally effective radiosurgical treatment of these brain metastases.

The recent analysis (2013) of a multi-institutional retrospective database of 383 patients with breast cancer demonstrated that tumor subtype is an essential factor resulting in large and significant differences in prognosis: after diagnosis of brain metastases, the median survival for the patients with the basal subtype (triple negative), Luminal A (ER/PR positive/HER2 negative), HER2 positive/ER/PR negative and Luminal B (triple positive) subtype were 7.3, 10, 17.9, and 22.9 months, respectively.[32] Another recent study from the Cleveland Clinic confirmed in 264 radiosurgically treated breast cancer patients with brain metastases a more favorable outcome in HER2+ patients relative to those with HER2− breast cancer, with a median survival of 31.3 vs. 14.1 months ($p < 0.01$).[98] Similarly, the presence of triple negative phenotype was associated with worse prognosis with median survival times after Gamma Knife radiosurgery being 6 vs. 16 months, respectively.[33] Most series do not define tumor subtypes; as a consequence it is now difficult to compare their results with respect to survival rates.

Lung cancer

Patients with a complete response after multimodality therapy for locally advanced non-small cell lung cancer (NSCLC) are at high risk for the subsequent development of brain metastases. Chen

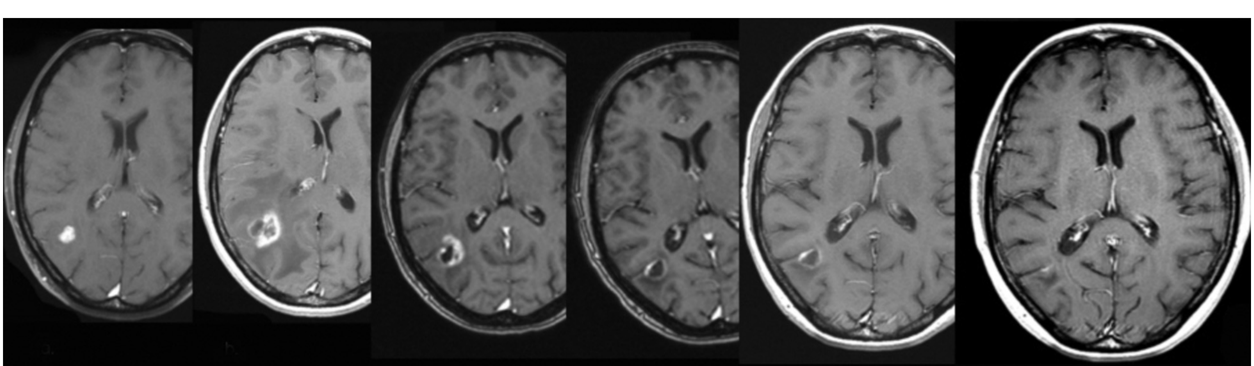

Fig. 2. Colon cancer: Gamma Knife treatment of a solitary metastasis: (a) before radiosurgery (b) 6 month FU, (c) 9 mo, (d)12 mo, (e)15 mo, (f) 61 months follow-up. Transient adverse radiation effect with edema 6 months after treatment and long-term tumor control 5 years after radiosurgery.

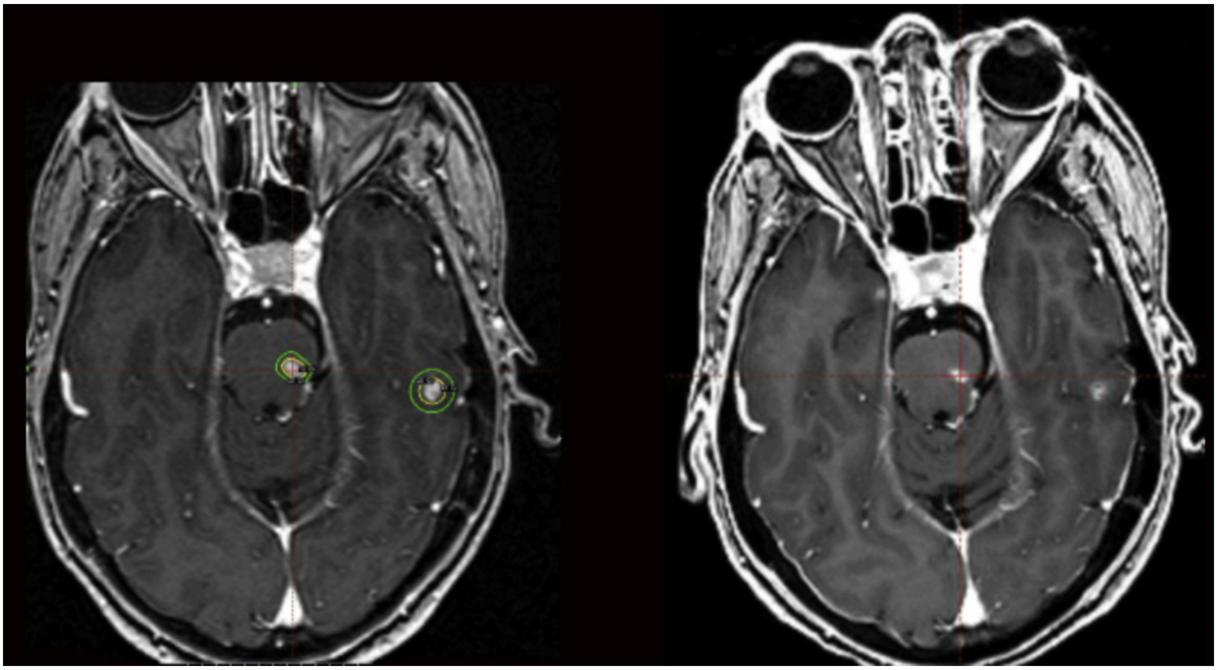

Fig. 3. multiple brain metastases from breast cancer: (a) Gamma Knife treatment of six metastases (here pons and left temporal) (b) MR follow- 3.5 years later, asymptomatic patient.

found that 55% developed brain metastases.[99] The 5-year estimates of brain metastasis-free survival for patients with squamous and nonsquamous cancers were 57% and 34%, respectively.[99] Median survival appears to be longer for a subgroup of NSCLC patients with mutations in the epidermal growth factor receptor that predict unique sensitivity to EGFR tyrosine kinase inhibitors (14.5 vs. 7.6 months, $P = .09$).[35]

Local control rates after stereotactic radiosurgery in general were quite consistent: between 81%,[100,101] 85%,[58] 94%[56] and 98%.[102] Tumor control rates after Gamma Knife radiosurgery varied depending on the tumor volume: Between 94% for metastases between 0.5 and 2 cm^3 and 85.7% for tumors between 8 and 14 $cm,^3$ respectively[64] with better result when minimum doses of $\geqslant$18 Gy are applied.[87] The median survival for patients with brain metastases from lung cancer treated with Gamma Knife ranged between 9 and 18 months.[56,58,64,70,101–105] A median overall survival of 18 months was reported in solitary brain metastasis from NSCLC after Gamma Knife treatment plus additional WBRT (in 78%)[106], but generally the combination of WBRT plus Gamma Knife did not provide better survival than Gamma Knife treatment alone.[64,70,103] The factors: younger age, good performance status, lung resection, no other systemic metastases, and either tumor resection or stereotactic radiosurgery predicted best survival.[64,107] Gamma Knife appears to be as effective in treating brain metastases from SCLC as for those from NSCLC.[102,108]

Malignant melanoma

Based on the limited local tumor control rate after WBRT, brain metastases of malignant melanoma are considered radioresistant. This restriction does not apply to radiosurgery, since various series after Gamma Knife radiosurgery of malignant melanoma report reproducible local tumor control rates between 73% and 90%[55,61,62,109–115] and a short-term local control rate of 98% at 3 months.[116] A study after both Linac- and Gamma Knife-radiosurgery in 31 patients with brain metastases from renal cell carcinoma, melanoma, or sarcoma showed a 6-month actuarial tumor control of 68.8%.[117] One stereotactic Linac study of intracranial melanoma metastases reported an unusually low one-year local control of only 42.3% for tumors >2 cc and 75.2% for tumors $\leqslant$2 cc.[118] In this study 33% of patients had been treated with prescription doses of <18 Gy,[118] which must be considered as a relatively low dose. When the RPA classification[119,120] was applied in patients where Gamma Knife radiosurgery was the initial treatment, patients in RPA Class I survived a median of 14.5 months, compared with a median survival of 5 months for patients in RPA Class II or III.[111] In a combined group of patients with brain metastases of melanoma and renal cell carcinoma, the median survival was 23.5 months for patients in RPA Class I and 10.5 months for patients in RPA Class II or III.[109] The median survival was 22 months for patients with a solitary brain metastasis of malignant melanoma when the extracranial disease was controlled, and when immunotherapy was administered after Gamma Knife treatment.[115] The local tumor control rates of melanoma metastases treated with Linac radiosurgery were 72–84%.[80,121,122]

Renal cell carcinoma

While brain metastases of renal cell carcinoma are considered unresponsive to fractionated WBRT with a reported survival of only 3.0–4.4 months,[123] Gamma Knife treatment provided local control rates between 83% and 96%[110,124–129] with a resulting median survival between 9.5 and 13 months.[126–130] For Gamma Knife treated patients in RPA class I, the median survival was 18–24 months.[124,126] Linac radiosurgery resulted in local control rates of 68–93%.[117,121,131] The addition of WBRT did not prevent the development of new remote tumors in patients with renal cell cancer metastases.[125,132]

Colorectal cancer

Local tumor control was achieved in 84–96% in colorectal cancer metastases undergoing Gamma Knife radiosurgery while the addition of WBRT to radiosurgery did not improve survival and local tumor control rates.[133–136]

Comparison with open surgery

If neurological symptoms are caused by the mass effect of a larger metastasis (>8–10 cm,[3]) the tumor is generally removed with a surgical resection. The expected median survival after surgery is 5.6–8.5 months[137–139], but a good performance status and controlled systemic disease are prerequisites for operability[140] and for potential survival benefits from surgery.[17] Local postoperative tumor recurrences occur in 46–58%[25,139,140] and postoperative conventional radiotherapy is applied to reduce this risk.[18] However, this combined approach does not improve the survival time and is both invasive and time consuming for the patient.[25,141] Three retrospective and one prospective randomized study compared the efficacy of Gamma Knife radiosurgery of brain metastases with open microsurgery (plus WBRT).[63,69,140,142] Similar to the three retrospective studies, even the prospective randomized study[142] showed equivalent outcomes after Gamma Knife radiosurgery vs. surgical resection plus WBRT as treatment results did not differ significantly in terms of survival, neurological death rates, and freedom from local recurrence.[142] Radiosurgery was associated with a shorter hospital stay, less frequent and shorter steroid application, and lower frequency of toxicities.[142] However, the randomized study comprises of only 64 patients and has been criticized as being too underpowered[20] for definite conclusions. In summary, the therapeutic efficacy of Gamma Knife radiosurgery can be considered as equivalent to standard surgical approaches in the treatment of smaller brain metastases that do not cause clinically relevant mass effect.[21]

Multiple metastases

A variety of MRI imaging protocols and even CT are applied in the diagnosis of brain metastases. Since the resulting number of detected tumors is directly dependent on the diagnostic method,[143] clinical results can hardly be classified according to numbers of treated metastases unless the diagnostic tools are standardized.

In most patients with multiple metastases, tumors tend to be small and do not affect the patient via local mass effect. Rather than the number of metastases, the total tumor volume appears to have an important influence on the prognosis.[144,145] In general there is a tendency to treat a larger number of brain metastases in a single radiosurgical session, since numerous studies document high local control after radiosurgical treatment of more than three brain metastases. Gamma Knife treatment in patients with 3–6 brain metastases provided actuarial 2-year control rates of 74.3%.[146] Serizawa and Yamamoto published a combined series of 1508 consecutive cases and reported no difference in survival between patients with 2–4 and 5–10 brain metastases.[147] In an earlier series of 521 patients treated with Gamma Knife, a similar outcome in terms of overall and neurological survival was found for patients with few ($\leqslant 3$) and many (4–10) brain metastases.[148] The number of brain metastases did not have a significant impact on survival,[149,150,65,85] which was confirmed after Gamma Knife treatment of patients with breast[52] and renal cancer.[132] In a cohort of 251 patients who had initially been treated with Gamma Knife alone at the MD Anderson Cancer Center it was shown that the number of brain metastases was not predictive of distant brain failure, local control, and overall survival.[151] Similarly, in a retrospective analysis total of 310 patients who had been treated with Gamma Knife radiosurgery after prior WBRT at the Stanford University School of Medicine there was no relationship between the number of brain metastases and survival after excluding patients with single metastases.[152] Patients who had undergone Gamma Knife radiosurgery at the Yonsei University College of Medicine, Seoul ($n = 323$) were divided into groups according to the number of lesions visible on MR images: Median survival was 10 months for patients with 1–5 metastases; 10 months for 6–10 lesions, 13 months for 11–15 lesions and 8 months for patients with more than 15 brain metastases.[153] The difference was not statistically significant.

Yamamoto and colleagues recently published a retrospective cohort study of patients who had undergone stereotactic radiosurgery without WBRT and demonstrated that the median survival time after radiosurgery was 7.9 months in patients with 1–4 brain metastases ($n = 548$), and 7 months in patients with more than four metastases ($n = 548$) ($p = 0.01$).[154] Some series indicate a less favorable median survival for patients with more than three[155,156] or more than seven metastases,[157] but there is no simplistic correlation between the number of metastases and the patient's prognosis. Hence, an increased number of brain metastases can be an unfavorable factor for longer survival, but the impact on survival time appears to be rather limited (Fig. 3). There is increasing evidence that other factors such as the subtype of the primary cancer[32–35] and the state of the systemic disease[36] are major contributing factors for the prognosis.

Patients with more than four brain metastases do not appear to have an inferior outcome in terms of neurological death, repeat SRS, maintenance of good neurological state and radiosurgery-related complications[154], but several treatment recommendations and practice guidelines limit the number of brain metastases that can be treated with radiosurgery to a virtually arbitrary number of three or four without consideration of tumor volume or diagnostic method. These recommendations are primarily based on level I evidence and hence on the available three randomized studies,[27,31,158] where the analysis was limited to patients with less than 3–4 metastases according to the studies' selection criteria: patients with a larger number of metastases had been excluded from evaluation.

Following a common (mis-)interpretation of the existing data, radiosurgical treatments are sometimes declined in patients with more than three metastases despite a realistic option of an effective local tumor control. However, there is no documented evidence for a lack of radiosurgical efficacy in multiple metastases or for the existence of another superior treatment for this condition.

Quality of life

Patients receiving stereotactic radiosurgery alone were at significantly lower risk of a decline in learning and memory function by 4 months when compared to patients undergoing additional WBRT.[29] The conclusion from this study was interpreted as level I evidence to support the use of stereotactic radiosurgery alone. Fractionated cranial irradiation causes a negative impact on health-related quality of life scales particularly due to fatigue and hair loss[159] and causes cognitive dysfunction immediately after the beginning of radiotherapy. Subacute radiation effects on verbal memory function are observed, both after therapeutic and prophylactic cranial irradiation.[160] These effects were more pronounced in patients with above-average performance at baseline.[160] A recently published prospective randomized EORTC phase III trial with 359 patients showed that WBRT after surgery or radiosurgery of brain metastases negatively impacted the health-related quality-of-life.[30] Delayed significant CNS toxicity 72 months after fractionated radiotherapy is a known phenomenon.[161] It was shown in a smaller prospective study after Gamma

Knife treatment for brain metastases that quality of life parameters remained either unchanged or improved in patients who had no evidence of intracranial or extracranial tumor progression.[162] Quality of life was also analyzed as part of the prospective randomized analysis RTOG 95–08. At 6 months follow-up a statistically significant improvement in clinical performance and decreased steroid use was found in the stereotactic radiosurgery boost treatment group when compared with the patients who had been treated by fractionated radiotherapy only.[31]

Fractionated radiotherapy or stereotactic radiosurgery

Only few studies compared the results after stereotactic radiosurgery directly with WBRT, but brain control and local control in Linac treated patients with 1–3 metastases were better after stereotactic radiosurgery than WBRT for patients in RPA Classes 1 and 2, whereas overall survival and distant control did not differ significantly.[163] A three-arm prospective randomized clinical trial compared Gamma Knife radiosurgery alone, WBRT alone or the combination of both in patients with brain metastases of various primary cancer histologies. The local control was 87%, 91%, and 62% for GK, GK + WBRT and WBRT alone respectively, suggesting that the outcome of the two radiosurgery arms were superior.[158] NSCLC patients with 1–10 brain metastases were treated with Gamma Knife radiosurgery or WBRT and neurological and qualitative survival were shown to be longer for the Gamma Knife group.[164] So far no study after conventional fractionated radiotherapy alone has ever shown superior results regarding local control or survival.

Three endpoints are important to determine the value of the combination of fractionated radiotherapy and radiosurgery: (a) survival, (b) local control of the treated metastases and (c) avoidance of new remote metastases.

WBRT plus radiosurgery: endpoint local control

The local control of metastases treated with stereotactic radiosurgery depends on the minimum tumor dose (prescription dose), which should be $\geq$18 Gy.[71] When radiosurgical prescription doses of less than 16 Gy were given, 27–38% of lesions failed locally.[165,166] With radiosurgical prescription doses >16 Gy, additional WBRT did not improve local control.[166] Several Linac series treated patients very close to this threshold of efficacy with mean prescription doses of 16–19 Gy.[81,118] Aoyama published a randomized controlled trial of patients with 1–4 brain metastases with an actuarial local tumor control rate of 88.7% at 12 months in the WBRT + SRS group and 72.5% in the SRS-alone group with similar preservation of neurologic function in both arms.[28] Another Linac study showed an improvement of 1-year- local control rates in combination of WBRT + SRS,[167] but several large retrospective studies have not documented any differences in local control of the radiosurgically treated metastases when WBRT was omitted.[53,62,168,169] ASTRO stated in evidence-based guidelines that in good prognosis patients with multiple brain metastases (<4, <4 cm), radiosurgery boost when added to WBRT improves treated

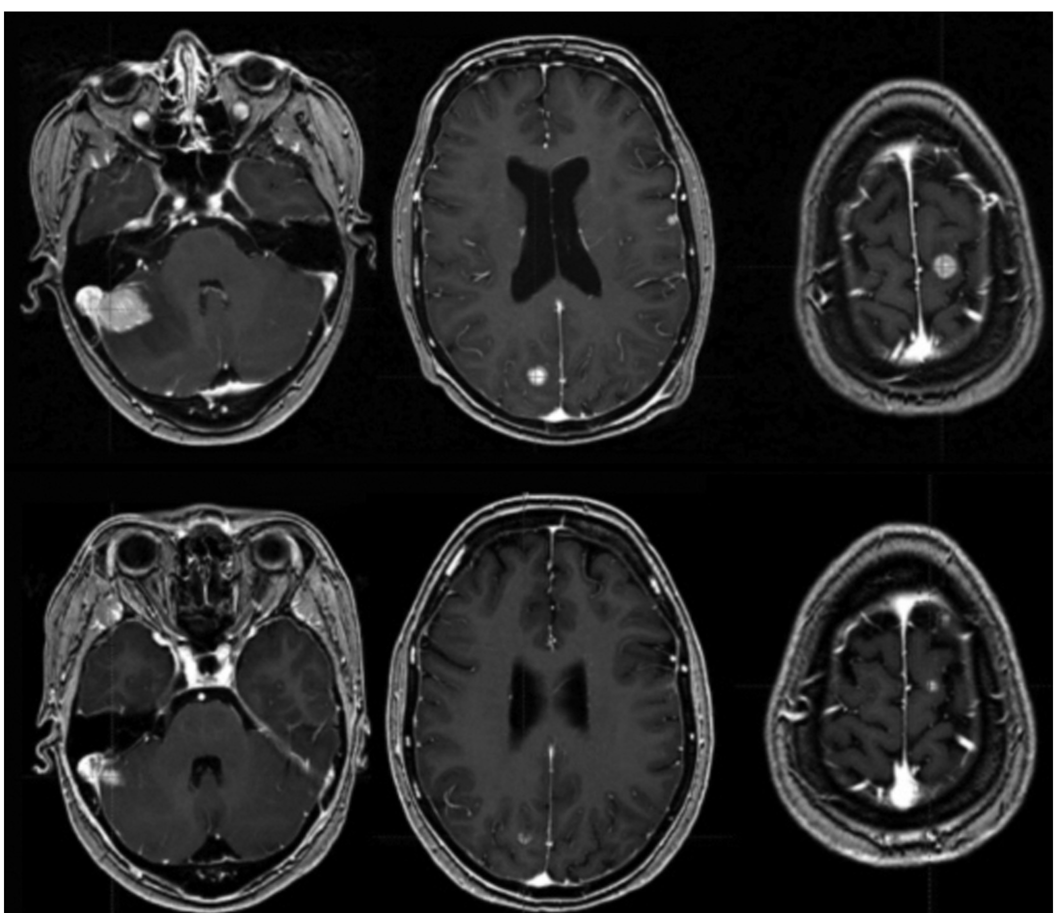

Fig. 4. A breast cancer: Recurrent multiple brain metastases after WBRT (a) before radiosurgery (b) MR-follow-up 3 months after Gamma Knife salvage treatment showing tumor shrinkage.

brain lesion and overall brain control as compared with WBRT alone.[170]

WBRT plus radiosurgery: endpoint survival

Radiosurgery can be applied for local recurrences or new metastases after WBRT[31,171] (Fig. 4). Chao reported a median survival of 17.7 months in a study with patients undergoing radiosurgery as salvage after initial WBRT.[172] This result appears to be superior to the vast majority of series of fractionated radiotherapy and offers new therapeutic options in case of failure after WBRT.

A prospective randomized study showed that the radiosurgical boost in addition to WBRT improved functional autonomy[31] and a multi-institutional retrospective study of 502 patients treated with WBRT and stereotactic radiosurgery boost (Linac or Gamma Knife) showed a median survival of 16.1, 10.3, and 8.7 months for RPA classes I, II, and III, respectively. The results were interpreted as a survival benefit in favor of the stereotactic radiosurgical boost when compared to historical RTOG data after WBRT.[66] In his randomized trial, Aoyama reported a median survival of 7.5 months in the WBRT + SRS group and 8.0 months for SRS alone.[28] Similarly, a retrospective Linac series showed no significant difference in 1-year-survival (53% vs. 56%) after SRS or WBRT + SRS.[167] Data from 10 institutions were used to compare survival probabilities of patients with brain metastases managed initially with stereotactic radiosurgery (SRS) alone vs. SRS + WBRT: The result was that omission of up-front WBRT did not compromise length of survival in patients treated with radiosurgery,[73] which was supported by others.[150,167,173]

Chidel analyzed the differentiated effect of the timing of fractionated radiotherapy after radiosurgery and found that patients treated with SRS who were treated with delayed WBRT at the time of a progression had the longest median survival (11.6 mo) when compared to patients with SRS and immediate WBRT. Differences, however, were not significant.[85] Prior WBRT might increase the risk for peritumoral edema in patients after radiosurgery[86] (Fig. 2) representing a potential contraindication only in large metastases.

WBRT and radiosurgery: endpoint distant failure

Since radiosurgery is a local treatment, a prophylactic effect against potential future brain metastases cannot be expected. Radiosurgically treated patients experience new metastases outside the initial target area in 39–52%,[85,158,174] when usually a new radiosurgical treatment remains an option.[75] Fractionated whole brain radiotherapy has been recommended to avoid new distant brain metastases. The theoretical argument was the intended treatment of the assumed microscopic disease in multiple metastases. However, several studies demonstrated that new distant brain metastases appear despite WBRT. A randomized controlled trial showed that even for patients who had been treated with fractionated whole brain radiotherapy (+SRS) the 12-month actuarial rate to develop new brain metastases was 41.5%.[28] Chao showed that 45% of patients failed >6 months after WBRT.[172] Others reported new metastases after WBRT in 34%.[163] In renal cell cancer new metastases occurred both in radiosurgically and conventionally irradiated patients (46% vs. 50%).[125] The recent prospective randomized EORTC study 22,952–26,001 documented new distant brain metastases after radiosurgery (2-year relapse rate) in 33% of patients who had been treated with WBRT.[26]

Although the risk for new brain metastases at distant sites is ca 15% lower after WBRT,[26] WBRT will not prevent new tumors. Consequently, new brain metastases must be expected in a considerable amount of patients despite WBRT. In this situation, WBRT can rarely be repeated while salvage radiosurgery remains an option.[91–93,172]

Summary

While the prognosis of patients with brain metastases depends primarily on the status of the systemic disease and hence on effectiveness of a systemic therapy, chemotherapies are still not sufficiently reliable as treatment options for brain metastases. Rapidly increasing evidence demonstrates that stereotactic radiosurgery provides highly effective and predictable local tumour control for single and multiple brain metastases. This accounts even for conventionally radioresistant metastases from melanoma or renal cancer. Gamma Knife represents the largest amount of published data, but so far there is no scientific evidence for clinical superiority of any technology in the treatment of brain metastases. Empirical dose and volume thresholds have been established for single session radiosurgery with low risk for side effects or local recurrences. Minimum doses of $\geq$18 Gy and a high radiation conformity should be applied. After radiosurgery, the reported local tumor control rates are 90–94% for brain metastases from breast cancer and 81–98% for brain metastases from lung cancer. In conventionally radioresistant brain metastases, local tumor control rates after radiosurgery are 73–90% for melanoma and 83–96% for renal cell cancer. Avoidance of WBRT can have a positive impact on the patient's cognitive status and health related quality of life (level I evidence). Hence, stereotactic radiosurgery can contribute to the patient's preserved functional integrity, when it replaces WBRT. There is a tendency to treat a larger number of brain metastases in a single radiosurgical session, since numerous studies document high local control after Gamma Knife treatment for >3 brain metastases. New remote brain metastases are reported in 33–42% after WBRT and in 39–52% after radiosurgery. Radiosurgery can be applied for local recurrences or new metastases after WBRT. While larger metastases (>8–10 cc) should be resected, Gamma Knife is equally effective as surgical approaches in treatment of smaller metastases (level I evidence). Radiosurgery can be repeated for new metastases provided the tumour volume remains below established limits. Hence radiological follow-up of treated patients with brain metastases is paramount.

Conflict of interest statement

None.

References

1. Schouten LJ, Rutten J, Huveneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer* 2002;**94**(10):2698–705.
2. Langley RE, Stephens RJ, Nankivell M, et al. Interim data from the Medical Research Council QUARTZ Trial: does whole brain radiotherapy affect the survival and quality of life of patients with brain metastases from non-small cell lung cancer? *Clin Oncol (R Coll Radiol)* 2013;**25**(3):e23–30.
3. Tsao MN, Rades D, Wirth A, et al. International practice survey on the management of brain metastases: third international consensus workshop on palliative radiotherapy and symptom control. *Clin Oncol (R Coll Radiol)* 2012;**24**(6):e81–92.
4. Chatani M, Teshima T, Hata K, Inoue T, Suzuki T. Whole brain irradiation for metastases from lung carcinoma. A clinical investigation. *Acta Radiol Oncol* 1985;**24**(4):311–4.
5. Chatani M, Matayoshi Y, Masaki N, Inoue T. Radiation therapy for brain metastases from lung carcinoma. Prospective randomized trial according to the level of lactate dehydrogenase. *Strahlenther Onkol* 1994;**170**(3):155–61.
6. Harwood AR, Simson WJ. Radiation therapy of cerebral metastases: a randomized prospective clinical trial. *Int J Radiat Oncol Biol Phys* 1977;**2**(11–):1091–4.
7. Kurtz JM, Gelber R, Brady LW, Carella RJ, Cooper JS. The palliation of brain metastases in a favorable patient population: a randomized clinical trial by the radiation therapy oncology group. *Int J Radiat Oncol Biol Phys* 1981;**7**(7):891–5.

8. Murray KJ, Scott C, Greenberg HM, et al. A randomized phase III study of accelerated hyperfractionation versus standard in patients with unresected brain metastases: a report of the radiation therapy oncology group (RTOG) 9104. *Int J Radiat Oncol Biol Phys* 1997;**39**(3):571–4.
9. Nieder C, Thamm R, Astner ST, Geinitz H, Molls M. Is whole-brain radiotherapy effective and safe in elderly patients with brain metastases? *Oncology* 2007;**72**(5–6):326–9.
10. Nieder C, Andratschke N, Grosu AL, Molls M. Recursive partitioning analysis (RPA) class does not predict survival in patients with four or more brain metastases. *Strahlenther Onkol* 2003;**179**(1):16–20.
11. Nussbaum ES, Djalilian HR, Cho KH, Hall WA. Brain metastases. Histology, multiplicity, surgery, and survival. *Cancer* 1996;**78**(8):1781–8.
12. Priestman TJ, Dunn J, Brada M, Rampling R, Baker PG. Final results of the Royal College of Radiologists' trial comparing two different radiotherapy schedules in the treatment of cerebral metastases. *Clin Oncol (R Coll Radiol)* 1996;**8**(5):308–15.
13. Nieder C, Norum J, Dalhaug A, Aandahl G, Pawinski A. Radiotherapy versus best supportive care in patients with brain metastases and adverse prognostic factors. *Clin Exp Metastasis* 2013 Epub ahead of print.
14. Suh JH, Stea B, Nabid A, et al. Phase III study of efaproxiral as an adjunct to whole-brain radiation therapy for brain metastases. *J Clin Oncol* 2006;**24**(1):106–14.
15. Tsao MN, Lloyd NS, Wong RK, Rakovitch E, Chow E, Laperriere N. Radiotherapeutic management of brain metastases: a systematic review and meta-analysis. *Cancer Treat Rev* 2005;**31**(4):256–73.
16. Heisterkamp C, Haatanen T, Schild SE, Rades D. Dose escalation in patients receiving whole-brain radiotherapy for brain metastases from colorectal cancer. *Strahlenther Onkol* 2010;**186**(2):70–5.
17. Soffietti R, Cornu P, Delattre JY, et al. EFNS Guidelines on diagnosis and treatment of brain metastases: report of an EFNS Task Force. *Eur J Neurol* 2006;**13**(7):674–81.
18. Kalkanis SN, Kondziolka D, Gaspar LE, et al. The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol* 2010;**96**(1):33–43.
19. Feyer P, Sautter-Bihl ML, Budach W, et al. DEGRO Practical Guidelines for palliative radiotherapy of breast cancer patients: brain metastases and leptomeningeal carcinomatosis. *Strahlenther Onkol* 2010;**186**(2):63–9.
20. Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Gaspar LE, et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An American Society for Radiation Oncology evidence-based guideline. *Pract Radiat Oncol* 2012;**2**:210–25.
21. Linskey ME, Andrews DW, Asher AL, et al. The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol* 2010;**96**(1):45–68.
22. Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol* 1993;**33**(6):583–90.
23. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990;**322**(8): 494–500.
24. Halasz LM, Weeks JC, Neville BA, Taback N, Punglia RS. Use of stereotactic radiosurgery for brain metastases from non-small cell lung cancer in the United States. *Int J Radiat Oncol Biol Phys* 2013;**85**(2):e109–16.
25. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* 1998;**280**(17):1485–9.
26. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22,952–26,001 study. *J Clin Oncol* 2011;**29**(2):134–41.
27. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys* 1999;**45**(2):427–34.
28. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* 2006;**295**(21):2483–91.
29. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* 2009;**10**(11):1037–44.
30. Soffietti R, Kocher M, Abacioglu UM, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. *J Clin Oncol* 2013;**31**(1):65–72.
31. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004;**363**(9422):1665–72.
32. Sperduto PW, Kased N, Roberge D, et al. The effect of tumor subtype on the time from primary diagnosis to development of brain metastases and survival in patients with breast cancer. *J Neurooncol* 2013;**112**(3):467–72.
33. Xu Z, Schlesinger D, Toulmin S, Rich T, Sheehan J. Impact of triple-negative phenotype on prognosis of patients with breast cancer brain metastases. *Int J Radiat Oncol Biol Phys* 2012;**84**(3):612–8.
34. Sperduto PW, Chao ST, Sneed PK, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4259 patients. *Int J Radiat Oncol Biol Phys* 2010;**77**(3):655–61.
35. Eichler AF, Kahle KT, Wang DL, et al. EGFR mutation status and survival after diagnosis of brain metastasis in nonsmall cell lung cancer. *Neuro Oncol* 2010;**12**(11):1193–9.
36. Lippitz BE. Cytokine patterns in patients with cancer: a systematic review. *Lancet Oncol* 2013;**14**(6):e218–28.
37. Barnett GH, Linskey ME, Adler JR, et al. Stereotactic radiosurgery – an organized neurosurgery-sanctioned definition. *J Neurosurg* 2007;**106**(1):1–5.
38. American Society for Radiation Oncology (2007) Stereotactic radiosurgery definition. Int J Radiat Oncol Biol Phys 2007;67(4):1280.
39. Lindquist C, Paddick I. The Leksell Gamma Knife Perfexion and comparisons with its predecessors. *Neurosurgery* 2007;**61**(Suppl. 3):130–40 discussion 40–1.
40. Mack A, Czempiel H, Kreiner HJ, Durr G, Wowra B. Quality assurance in stereotactic space: a system test for verifying the accuracy of aim in radiosurgery. *Med Phys* 2002;**29**(4):561–8.
41. Chang SD, Main W, Martin DP, Gibbs IC, Heilbrun MP. An analysis of the accuracy of the cyberknife: a robotic frameless stereotactic radiosurgical system. *Neurosurgery* 2003;**52**(1):140–6 discussion 46–7.
42. Murphy MJ, Cox RS. The accuracy of dose localization for an image-guided frameless radiosurgery system. *Med Phys* 1996;**23**(12):2043–9.
43. Murphy MJ. Intrafraction geometric uncertainties in frameless image-guided radiosurgery. *Int J Radiat Oncol Biol Phys* 2009;**73**(5):1364–8.
44. Verellen D, Linthout N, Bel A, et al. Assessment of the uncertainties in dose delivery of a commercial system for linac-based stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys* 1999;**44**(2):421–33.
45. Papagiannis P, Karaiskos P, Kozicki M, et al. Three-dimensional dose verification of the clinical application of gamma knife stereotactic radiosurgery using polymer gel and MRI. *Phys Med Biol* 2005;**50**(9): 1979–90.
46. Nedzi LA, Kooy HM, Alexander 3rd E, Svensson GK, Loeffler JS. Dynamic field shaping for stereotactic radiosurgery: a modeling study. *Int J Radiat Oncol Biol Phys* 1993;**25**(5):859–69.
47. Kubo HD, Wilder RB, Pappas CT. Impact of collimator leaf width on stereotactic radiosurgery and 3D conformal radiotherapy treatment plans. *Int J Radiat Oncol Biol Phys* 1999;**44**(4):937–45.
48. Zytkovicz A, Daftari I, Phillips TL, Chuang CF, Verhey L, Petti PL. Peripheral dose in ocular treatments with CyberKnife and Gamma Knife radiosurgery compared to proton radiotherapy. *Phys Med Biol* 2007;**52**(19):5957–71.
49. Regis J, Tamura M, Guillot C, et al. Radiosurgery with the world's first fully robotized Leksell Gamma Knife PerfeXion in clinical use: a 200-patient prospective, randomized, controlled comparison with the Gamma Knife 4C. *Neurosurgery* 2009;**64**(2):346–55 discussion 55–6.
50. Sturm V, Kober B, Hover KH, et al. Stereotactic percutaneous single dose irradiation of brain metastases with a linear accelerator. *Int J Radiat Oncol Biol Phys* 1987;**13**(2):279–82.
51. Lindquist C. Gamma knife surgery for recurrent solitary metastasis of a cerebral hypernephroma: case report. *Neurosurgery* 1989;**25**(5):802–4.
52. Amendola BE, Wolf AL, Coy SR, Amendola M, Bloch L. Gamma knife radiosurgery in the treatment of patients with single and multiple brain metastases from carcinoma of the breast. *Cancer J* 2000;**6**(2):88–92.
53. Chen JC, O'Day S, Morton D, et al. Stereotactic radiosurgery in the treatment of metastatic disease to the brain. *Stereotact Funct Neurosurg* 1999;**73**(1–4):60–3.
54. Firlik KS, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for brain metastases from breast cancer. *Ann Surg Oncol* 2000;**7**(5):333–8.
55. Gaudy-Marqueste C, Regis JM, Muracciole X, et al. Gamma-Knife radiosurgery in the management of melanoma patients with brain metastases: a series of 106 patients without whole-brain radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;**65**(3):809–16.
56. Gerosa M, Nicolato A, Foroni R, Tomazzoli L, Bricolo A. Analysis of long-term outcomes and prognostic factors in patients with non-small cell lung cancer brain metastases treated by gamma knife radiosurgery. *J Neurosurg* 2005;**102**(Suppl):75–80.
57. Hasegawa T, Kondziolka D, Flickinger JC, Germanwala A, Lunsford LD. Brain metastases treated with radiosurgery alone: an alternative to whole brain radiotherapy? *Neurosurgery* 2003;**52**(6):1318–26 [discussion 26].
58. Kim YS, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for patients with nonsmall cell lung carcinoma metastatic to the brain. *Cancer* 1997;**80**(11):2075–83.
59. Lavine SD, Petrovich Z, Cohen-Gadol AA, et al. Gamma knife radiosurgery for metastatic melanoma: an analysis of survival, outcome, and complications. *Neurosurgery* 1999;**44**(1):59–64 discussion 64–6.
60. Lippitz BE, Kraepelien T, Hautanen K, et al. Gamma knife radiosurgery for patients with multiple cerebral metastases. *Acta Neurochir Suppl* 2004;**91**: 79–87.
61. Mathieu D, Kondziolka D, Cooper PB, et al. Gamma knife radiosurgery in the management of malignant melanoma brain metastases. *Neurosurgery* 2007;**60**(3):471–81 discussion 81–2.
62. Mori Y, Kondziolka D, Flickinger JC, Kirkwood JM, Agarwala S, Lunsford LD. Stereotactic radiosurgery for cerebral metastatic melanoma: factors affecting local disease control and survival. *Int J Radiat Oncol Biol Phys* 1998;**42**(3): 581–9.

63. Muacevic A, Kreth FW, Horstmann GA, et al. Surgery and radiotherapy compared with gamma knife radiosurgery in the treatment of solitary cerebral metastases of small diameter. *J Neurosurg* 1999;**91**(1):35–43.
64. Pan HC, Sheehan J, Stroila M, Steiner M, Steiner L. Gamma knife surgery for brain metastases from lung cancer. *J Neurosurg* 2005;**102**(Suppl):128–33.
65. Petrovich Z, Yu C, Giannotta SL, O'Day S, Apuzzo ML. Survival and pattern of failure in brain metastasis treated with stereotactic gamma knife radiosurgery. *J Neurosurg* 2002;**97**(5 Suppl):499–506.
66. Sanghavi SN, Miranpuri SS, Chappell R, et al. Radiosurgery for patients with brain metastases: a multi-institutional analysis, stratified by the RTOG recursive partitioning analysis method. *Int J Radiat Oncol Biol Phys* 2001;**51**(2): 426–34.
67. Sansur CA, Chin LS, Ames JW, et al. Gamma knife radiosurgery for the treatment of brain metastases. *Stereotact Funct Neurosurg* 2000;**74**(1):37–51.
68. Schoeggl A, Kitz K, Ertl A, Reddy M, Bavinzski G, Schneider B. Prognostic factor analysis for multiple brain metastases after gamma knife radiosurgery: results in 97 patients. *J Neurooncol* 1999;**42**(2):169–75.
69. Schoggl A, Kitz K, Reddy M, et al. Defining the role of stereotactic radiosurgery versus microsurgery in the treatment of single brain metastases. *Acta Neurochir* 2000;**142**(6):621–6.
70. Sheehan JP, Sun MH, Kondziolka D, Flickinger J, Lunsford LD. Radiosurgery for non-small cell lung carcinoma metastatic to the brain: long-term outcomes and prognostic factors influencing patient survival time and local tumor control. *J Neurosurg* 2002;**97**(6):1276–81.
71. Shiau CY, Sneed PK, Shu HK, et al. Radiosurgery for brain metastases: relationship of dose and pattern of enhancement to local control. *Int J Radiat Oncol Biol Phys* 1997;**37**(2):375–83.
72. Simonova G, Liscak R, Novotny Jr J, Novotny J. Solitary brain metastases treated with the Leksell Gamma Knife: prognostic factors for patients. *Radiother Oncol* 2000;**57**(2):207–13.
73. Sneed PK, Suh JH, Goetsch SJ, et al. A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. *Int J Radiat Oncol Biol Phys* 2002;**53**(3):519–26.
74. Wowra B, Horstmann GA, Cibis R, Czempiel H. Profile of ambulatory radiosurgery with the Gamma Knife system. 2: report of clinical experiences. *Radiologe* 1997;**37**(12):1003–15.
75. Wowra B, Siebels M, Muacevic A, Kreth FW, Mack A, Hofstetter A. Repeated gamma knife surgery for multiple brain metastases from renal cell carcinoma. *J Neurosurg* 2002;**97**(4):785–93.
76. Simonova G, Roman L. Radiosurgery in the treatment of malignant brain tumors. *Expert Rev Anticancer Ther* 2003;**3**(6):879–90.
77. Deinsberger R, Tidstrand J. LINAC radiosurgery as single treatment in cerebral metastases. *J Neurooncol* 2006;**76**(1):77–83.
78. Schomas DA, Roeske JC, MacDonald RL, Sweeney PJ, Mehta N, Mundt AJ. Predictors of tumor control in patients treated with linac-based stereotactic radiosurgery for metastatic disease to the brain. *Am J Clin Oncol* 2005;**28**(2): 180–7.
79. Voges J, Treuer H, Erdmann J, et al. Linac radiosurgery in brain metastases. *Acta Neurochir Suppl* 1994;**62**:72–6.
80. Herfarth KK, Izwekowa O, Thilmann C, et al. Linac-based radiosurgery of cerebral melanoma metastases. Analysis of 122 metastases treated in 64 patients. *Strahlenther Onkol* 2003;**179**(6):366–71.
81. Nataf F, Schlienger M, Liu Z, et al. Radiosurgery with or without a 2-mm margin for 93 single brain metastases. *Int J Radiat Oncol Biol Phys* 2008;**70**(3):766–72.
82. Kato T, Shirato H, Suzuki K, et al. Stereotactic irradiation for brain metastases using linear accelerator. *No Shinkei Geka* 1996;**24**(11):1003–9.
83. Hara W, Tran P, Li G, et al. Cyberknife for brain metastases of malignant melanoma and renal cell carcinoma. *Neurosurgery* 2009;**64**(Suppl. 2):A26–32.
84. Muacevic A, Kufeld M, Wowra B, Kreth FW, Tonn JC. Feasibility, safety, and outcome of frameless image-guided robotic radiosurgery for brain metastases. *J Neurooncol* 2010;**97**(2):267–74.
85. Chidel MA, Suh JH, Reddy CA, Chao ST, Lundbeck MF, Barnett GH. Application of recursive partitioning analysis and evaluation of the use of whole brain radiation among patients treated with stereotactic radiosurgery for newly diagnosed brain metastases. *Int J Radiat Oncol Biol Phys* 2000;**47**(4):993–9.
86. Pan HC, Sun MH, Chen CC, Chen CJ, Lee CH, Sheehan J. Neuroimaging and quality-of-life outcomes in patients with brain metastasis and peritumoral edema who undergo Gamma Knife surgery. *J Neurosurg* 2008;**109**(Suppl): 90–8.
87. Zabel A, Milker-Zabel S, Thilmann C, et al. Treatment of brain metastases in patients with non-small cell lung cancer (NSCLC) by stereotactic linac-based radiosurgery: prognostic factors. *Lung Cancer* 2002;**37**(1):87–94.
88. Karlsson B, Wersäll B, Lippitz B, Kihlström L. Repeated radiosurgery versus fractionated radiotherapy in the treatment of brain metastases from renal cell carcinoma. In: Kondziolka D, editor. *Radiosurgery*. Basel: Karger; 2000. p. 232–9.
89. Bartsch R, Fromm S, Rudas M, et al. Intensified local treatment and systemic therapy significantly increase survival in patients with brain metastases from advanced breast cancer – a retrospective analysis. *Radiother Oncol* 2006;**80**(3):313–7.
90. Ogura M, Mitsumori M, Okumura S, et al. Radiation therapy for brain metastases from breast cancer. *Breast Cancer* 2003;**10**(4):349–55.
91. Akyurek S, Chang EL, Mahajan A, et al. Stereotactic radiosurgical treatment of cerebral metastases arising from breast cancer. *Am J Clin Oncol* 2007;**30**(3): 310–4.
92. Lederman G, Wronski M, Fine M. Fractionated radiosurgery for brain metastases in 43 patients with breast carcinoma. *Breast Cancer Res Treat* 2001;**65**(2):145–54.
93. Kondziolka D, Kano H, Harrison GL, et al. Stereotactic radiosurgery as primary and salvage treatment for brain metastases from breast cancer. Clinical article. *J Neurosurg* 2011;**114**(3):792–800.
94. Muacevic A, Kreth FW, Tonn JC, Wowra B. Stereotactic radiosurgery for multiple brain metastases from breast carcinoma. *Cancer* 2004;**100**(8): 1705–11.
95. Goyal S, Prasad D, Harrell Jr F, Matsumoto J, Rich T, Steiner L. Gamma knife surgery for the treatment of intracranial metastases from breast cancer. *J Neurosurg* 2005;**103**(2):218–23.
96. Levin KJ, Youssef EF, Sloan AE, Patel R, Zabad RK, Zamorano L. Gamma knife radiosurgery in patients with advanced breast cancer undergoing bone marrow transplant. *J Neurosurg* 2002;**97**(5 Suppl.):663–5.
97. Kased N, Binder DK, McDermott MW, et al. Gamma Knife radiosurgery for brain metastases from primary breast cancer. *Int J Radiat Oncol Biol Phys* 2009;**75**(4):1132–40.
98. Xu Z, Marko NF, Chao ST, et al. Relationship between HER2 status and prognosis in women with brain metastases from breast cancer. *Int J Radiat Oncol Biol Phys* 2012;**82**(5):e739–47.
99. Chen AM, Jahan TM, Jablons DM, Garcia J, Larson DA. Risk of cerebral metastases and neurological death after pathological complete response to neoadjuvant therapy for locally advanced nonsmall-cell lung cancer: clinical implications for the subsequent management of the brain. *Cancer* 2007;**109**(8):1668–75.
100. Hoffman R, Sneed PK, McDermott MW, et al. Radiosurgery for brain metastases from primary lung carcinoma. *Cancer J* 2001;**7**(2):121–31.
101. Sheehan J, Kondziolka D, Flickinger J, Lunsford LD. Radiosurgery for patients with recurrent small cell lung carcinoma metastatic to the brain: outcomes and prognostic factors. *J Neurosurg* 2005;**102**(Suppl):247–54.
102. Serizawa T, Ono J, Iichi T, et al. Gamma knife radiosurgery for metastatic brain tumors from lung cancer: a comparison between small cell and non-small cell carcinoma. *J Neurosurg* 2002;**97**(5 Suppl):484–8.
103. Flannery TW, Suntharalingam M, Kwok Y, et al. Gamma knife stereotactic radiosurgery for synchronous versus metachronous solitary brain metastases from non-small cell lung cancer. *Lung Cancer* 2003;**42**(3):327–33.
104. Kong DS, Lee JI, Nam DH, et al. Prognosis of non-small cell lung cancer with synchronous brain metastases treated with gamma knife radiosurgery. *J Korean Med Sci* 2006;**21**(3):527–32.
105. Motta M, Del Vecchio A, Attuati L, et al. Gamma knife radiosurgery for treatment of cerebral metastases from non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011;**81**(4):e463–8.
106. Flannery TW, Suntharalingam M, Regine WF, et al. Long-term survival in patients with synchronous, solitary brain metastasis from non-small-cell lung cancer treated with radiosurgery. *Int J Radiat Oncol Biol Phys* 2008;**72**(1):19–23.
107. Moazami N, Rice TW, Rybicki LA, et al. Stage III non-small cell lung cancer and metachronous brain metastases. *J Thorac Cardiovasc Surg* 2002;**124**(1): 113–22.
108. Wegner RE, Olson AC, Kondziolka D, Niranjan A, Lundsford LD, Flickinger JC. Stereotactic radiosurgery for patients with brain metastases from small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011;**81**(3):e21–7.
109. Brown PD, Brown CA, Pollock BE, Gorman DA, Foote RL. Stereotactic radiosurgery for patients with "radioresistant" brain metastases. *Neurosurgery* 2008;**62**(Suppl.):790–801.
110. Powell JW, Chung CT, Shah HR, et al. Gamma Knife surgery in the management of radioresistant brain metastases in high-risk patients with melanoma, renal cell carcinoma, and sarcoma. *J Neurosurg* 2008;**109**(Suppl): 122–8.
111. Radbill AE, Fiveash JF, Falkenberg ET, et al. Initial treatment of melanoma brain metastases using gamma knife radiosurgery: an evaluation of efficacy and toxicity. *Cancer* 2004;**101**(4):825–33.
112. Seung SK, Sneed PK, McDermott MW, et al. Gamma knife radiosurgery for malignant melanoma brain metastases. *Cancer J Sci Am* 1998;**4**(2): 103–9.
113. Yu C, Chen JC, Apuzzo ML, et al. Metastatic melanoma to the brain: prognostic factors after gamma knife radiosurgery. *Int J Radiat Oncol Biol Phys* 2002;**52**(5):1277–87.
114. Mingione V, Oliveira M, Prasad D, Steiner M, Steiner L. Gamma surgery for melanoma metastases in the brain. *J Neurosurg* 2002;**96**(3):544–51.
115. Liew DN, Kano H, Kondziolka D, et al. Outcome predictors of Gamma Knife surgery for melanoma brain metastases. Clinical article. *J Neurosurg* 2011;**114**(3):769–79.
116. Grob JJ, Regis J, Laurans R, et al. Radiosurgery without whole brain radiotherapy in melanoma brain metastases. Club de Cancerologie Cutanee. *Eur J Cancer* 1998;**34**(8):1187–92.
117. Manon R, O'Neill A, Knisely J, et al. Phase II trial of radiosurgery for one to three newly diagnosed brain metastases from renal cell carcinoma, melanoma, and sarcoma: an Eastern Cooperative Oncology Group study (E 6397). *J Clin Oncol* 2005;**23**(34):8870–6.
118. Selek U, Chang EL, Hassenbusch 3rd SJ, et al. Stereotactic radiosurgical treatment in 103 patients for 153 cerebral melanoma metastases. *Int J Radiat Oncol Biol Phys* 2004;**59**(4):1097–106.
119. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three radiation therapy oncology group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 1997;**37**(4):745–51.

120. Tendulkar RD, Liu SW, Barnett GH, et al. RPA classification has prognostic significance for surgically resected single brain metastasis. *Int J Radiat Oncol Biol Phys* 2006;**66**(3):810–7.
121. Chang EL, Selek U, Hassenbusch 3rd SJ, et al. Outcome variation among "radioresistant" brain metastases treated with stereotactic radiosurgery. *Neurosurgery* 2005;**56**(5):936–45.
122. Noel G, Simon JM, Valery CA, et al. Linac radiosurgery for brain metastasis of melanoma. *Stereotact Funct Neurosurg* 2002;**79**(3–4):245–55.
123. Wronski M, Maor MH, Davis BJ, Sawaya R, Levin VA. External radiation of brain metastases from renal carcinoma: a retrospective study of 119 patients from the M.D. Anderson Cancer Center. *Int J Radiat Oncol Biol Phys* 1997;**37**(4):753–9.
124. Hernandez L, Zamorano L, Sloan A, et al. Gamma knife radiosurgery for renal cell carcinoma brain metastases. *J Neurosurg* 2002;**97**(5 Suppl):489–93.
125. Mori Y, Kondziolka D, Flickinger JC, Logan T, Lunsford LD. Stereotactic radiosurgery for brain metastasis from renal cell carcinoma. *Cancer* 1998;**83**(2):344–53.
126. Muacevic A, Kreth FW, Mack A, Tonn JC, Wowra B. Stereotactic radiosurgery without radiation therapy providing high local tumor control of multiple brain metastases from renal cell carcinoma. *Minim Invasive Neurosurg* 2004;**47**(4):203–8.
127. Sheehan JP, Sun MH, Kondziolka D, Flickinger J, Lunsford LD. Radiosurgery in patients with renal cell carcinoma metastasis to the brain: long-term outcomes and prognostic factors influencing survival and local tumor control. *J Neurosurg* 2003;**98**(2):342–9.
128. Shuto T, Inomori S, Fujino H, Nagano H. Gamma knife surgery for metastatic brain tumors from renal cell carcinoma. *J Neurosurg* 2006;**105**(4):555–60.
129. Marko NF, Angelov L, Toms SA, et al. Stereotactic radiosurgery as single-modality treatment of incidentally identified renal cell carcinoma brain metastases. *World Neurosurg* 2010;**73**(3):186–93 discussion e29.
130. Hoshi S, Jokura H, Nakamura H, et al. Gamma-knife radiosurgery for brain metastasis of renal cell carcinoma: results in 42 patients. *Int J Urol* 2002;**9**(11):618–25 discussion 26; author reply 27.
131. Noel G, Valery CA, Boisserie G, et al. LINAC radiosurgery for brain metastasis of renal cell carcinoma. *Urol Oncol* 2004;**22**(1):25–31.
132. Goyal LK, Suh JH, Reddy CA, Barnett GH. The role of whole brain radiotherapy and stereotactic radiosurgery on brain metastases from renal cell carcinoma. *Int J Radiat Oncol Biol Phys* 2000;**47**(4):1007–12.
133. Hasegawa T, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for brain metastases from gastrointestinal tract cancer. *Surg Neurol* 2003;**60**(6):506–14 discussion 14-5.
134. Schoeggl A, Kitz K, Reddy M, Zauner C. Stereotactic radiosurgery for brain metastases from colorectal cancer. *Int J Colorectal Dis* 2002;**17**(3):150–5.
135. Matsunaga S, Shuto T, Kawahara N, Suenaga J, Inomori S, Fujino H. Gamma Knife surgery for brain metastases from colorectal cancer. Clinical article. *J Neurosurg* 2011;**114**(3):782–9.
136. Da Silva AN, Nagayama K, Schlesinger DJ, Sheehan JP. Gamma Knife surgery for brain metastases from gastrointestinal cancer. *J Neurosurg* 2009;**111**(3):423–30.
137. Mintz AH, Kestle J, Rathbone MP, et al. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer* 1996;**78**(7):1470–6.
138. Paek SH, Audu PB, Sperling MR, Cho J, Andrews DW. Reevaluation of surgery for the treatment of brain metastases: review of 208 patients with single or multiple brain metastases treated at one institution with modern neurosurgical techniques. *Neurosurgery* 2005;**56**(5):1021–34 discussion 21–34.
139. Zacest AC, Besser M, Stevens G, Thompson JF, McCarthy WH, Culjak G. Surgical management of cerebral metastases from melanoma: outcome in 147 patients treated at a single institution over two decades. *J Neurosurg* 2002;**96**(3):552–8.
140. O'Neill BP, Iturria NJ, Link MJ, Pollock BE, Ballman KV, O'Fallon JR. A comparison of surgical resection and stereotactic radiosurgery in the treatment of solitary brain metastases. *Int J Radiat Oncol Biol Phys* 2003;**55**(5):1169–76.
141. Armstrong JG, Wronski M, Galicich J, Arbit E, Leibel SA, Burt M. Postoperative radiation for lung cancer metastatic to the brain. *J Clin Oncol* 1994;**12**(11):2340–4.
142. Muacevic A, Wowra B, Siefert A, Tonn JC, Steiger HJ, Kreth FW. Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre phase III trial. *J Neurooncol* 2008;**87**(3):299–307.
143. Hanssens P, Karlsson B, Yeo TT, Chou N, Beute G. Detection of brain micrometastases by high-resolution stereotactic magnetic resonance imaging and its impact on the timing of and risk for distant recurrences. *J Neurosurg* 2011;**115**(3):499–504.
144. Skeie BS, Skeie GO, Enger PO, et al. Gamma knife surgery in brain melanomas: absence of extracranial metastases and tumor volume strongest indicators of prolonged survival. *World Neurosurg* 2011;**75**(5–6):684–91.
145. Chen JC, Petrovich Z, O'Day S, et al. Stereotactic radiosurgery in the treatment of metastatic disease to the brain. *Neurosurgery* 2000;**47**(2):268–79 discussion 79–81.
146. Jawahar A, Shaya M, Campbell P, et al. Role of stereotactic radiosurgery as a primary treatment option in the management of newly diagnosed multiple (3–6) intracranial metastases. *Surg Neurol* 2005;**64**(3):207–12.
147. Serizawa T, Yamamoto M, Sato Y, et al. Gamma Knife surgery as sole treatment for multiple brain metastases: 2-center retrospective review of 1508 cases meeting the inclusion criteria of the JLGK0901 multi-institutional prospective study. *J Neurosurg* 2010;**113**(Suppl):48–52.
148. Serizawa T, Saeki N, Higuchi Y, et al. Gamma knife surgery for brain metastases: indications for and limitations of a local treatment protocol. *Acta Neurochir* 2005;**147**(7):721–6 discussion 26.
149. Yan ES, Sneed PK, McDermott MW, Kunwar S, Wara WM, Larson DA. Number of brain metastases is not an important prognostic factor for survival following radiosurgery for newly-diagnosed nonmelanoma brain metastases. *Int J Radiat Oncol Biol Phys* 2003;**57**(Suppl. 2):131–2.
150. Shu HK, Sneed PK, Shiau CY, et al. Factors influencing survival after gamma knife radiosurgery for patients with single and multiple brain metastases. *Cancer J Sci Am* 1996;**2**(6):335–42.
151. Likhacheva A, Pinnix CC, Parikh NR, et al. Predictors of survival in contemporary practice after initial radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys* 2013;**85**(3):656–61.
152. Caballero JA, Sneed PK, Lamborn KR, et al. Prognostic factors for survival in patients treated with stereotactic radiosurgery for recurrent brain metastases after prior whole brain radiotherapy. *Int J Radiat Oncol Biol Phys* 2012;**83**(1):303–9.
153. Chang WS, Kim HY, Chang JW, Park YG, Chang JH. Analysis of radiosurgical results in patients with brain metastases according to the number of brain lesions: is stereotactic radiosurgery effective for multiple brain metastases? *J Neurosurg* 2010;**113**(Suppl):73–8.
154. Yamamoto M, Kawabe T, Sato Y, et al. A case-matched study of stereotactic radiosurgery for patients with multiple brain metastases: comparing treatment results for 1-4 vs ⩾ 5 tumors. *J Neurosurg* 2013;**118**(6):1258–68.
155. DiLuna ML, King Jr JT, Knisely JP, Chiang VL. Prognostic factors for survival after stereotactic radiosurgery vary with the number of cerebral metastases. *Cancer* 2007;**109**(1):135–45.
156. Nam TK, Lee JI, Jung YJ, et al. Gamma knife surgery for brain metastases in patients harboring four or more lesions: survival and prognostic factors. *J Neurosurg* 2005;**102**(Suppl.):147–50.
157. Bhatnagar AK, Kondziolka D, Lunsford LD, Flickinger JC. Recursive partitioning analysis of prognostic factors for patients with four or more intracranial metastases treated with radiosurgery. *Technol Cancer Res Treat* 2007;**6**(3):153–60.
158. Chougule PB, Burton-Williams M, Saris S, et al. Randomized treatment of brain metastasis with gamma knife radiosurgery, whole brain radiotherapy or both. *Int J Radiat Oncol Biol Phys* 2000;**48**(Suppl. 3):114.
159. Slotman BJ, Mauer ME, Bottomley A, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC radiation oncology and lung cancer groups. *J Clin Oncol* 2009;**27**(1):78–84.
160. Welzel G, Fleckenstein K, Schaefer J, et al. Memory function before and after whole brain radiotherapy in patients with and without brain metastases. *Int J Radiat Oncol Biol Phys* 2008;**72**(5):1311–8.
161. Doyle DM, Einhorn LH. Delayed effects of whole brain radiotherapy in germ cell tumor patients with central nervous system metastases. *Int J Radiat Oncol Biol Phys* 2008;**70**(5):1361–4.
162. DiBiase SJ, Chin LS, Ma L. Influence of gamma knife radiosurgery on the quality of life in patients with brain metastases. *Am J Clin Oncol* 2002;**25**(2):131–4.
163. Rades D, Pluemer A, Veninga T, Hanssens P, Dunst J, Schild SE. Whole-brain radiotherapy versus stereotactic radiosurgery for patients in recursive partitioning analysis classes 1 and 2 with 1 to 3 brain metastases. *Cancer* 2007;**110**(10):2285–92.
164. Serizawa T, Iuchi T, Ono J, et al. Gamma knife treatment for multiple metastatic brain tumors compared with whole-brain radiation therapy. *J Neurosurg* 2000;**93**(Suppl. 3):32–6.
165. Jawahar A, Matthew RE, Minagar A, et al. Gamma knife surgery in the management of brain metastases from lung carcinoma: a retrospective analysis of survival, local tumor control, and freedom from new brain metastasis. *J Neurosurg* 2004;**100**(5):842–7.
166. Varlotto JM, Flickinger JC, Niranjan A, Bhatnagar A, Kondziolka D, Lunsford LD. The impact of whole-brain radiation therapy on the long-term control and morbidity of patients surviving more than one year after gamma knife radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys* 2005;**62**(4):1125–32.
167. Rades D, Kueter JD, Hornung D, et al. Comparison of stereotactic radiosurgery (SRS) alone and whole brain radiotherapy (WBRT) plus a stereotactic boost (WBRT+SRS) for one to three brain metastases. *Strahlenther Onkol* 2008;**184**(12):655–62.
168. Sneed PK, Lamborn KR, Forstner JM, et al. Radiosurgery for brain metastases: is whole brain radiotherapy necessary? *Int J Radiat Oncol Biol Phys* 1999;**43**(3):549–58.
169. Flickinger JC, Kondziolka D, Lunsford LD, et al. A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis. *Int J Radiat Oncol Biol Phys* 1994;**28**(4):797–802.
170. Mehta MP, Tsao MN, Whelan TJ, et al. The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys* 2005;**63**(1):37–46.

171. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90–05. *Int J Radiat Oncol Biol Phys* 2000;**47**(2):291–8.
172. Chao ST, Barnett GH, Vogelbaum MA, et al. Salvage stereotactic radiosurgery effectively treats recurrences from whole-brain radiation therapy. *Cancer* 2008;**113**(8):2198–204.
173. Pirzkall A, Debus J, Lohr F, et al. Radiosurgery alone or in combination with whole-brain radiotherapy for brain metastases. *J Clin Oncol* 1998;**16**(11): 3563–9.
174. Shirato H, Takamura A, Tomita M, et al. Stereotactic irradiation without whole-brain irradiation for single brain metastasis. *Int J Radiat Oncol Biol Phys* 1997;**37**(2):385–91.